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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/541,626	HANAWA, HARUO	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 1977*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *7-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 17-20* is/are rejected.

7)☒ Claim(s) *5 and 6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 July 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *t*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 11/1/07.

Claims 17-20 were added.

Claims 7-16 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/26/07.

Claims 1-6 and 17-20 are under consideration.

Rejections not reiterated are withdrawn.

Claim Objections

As pointed out by Applicant at page 14 of the response, claims 5 and 6 were improperly objected to in the last Action. These claims were amended by preliminary amendment to depend solely from claim 1, and were not improperly multiply dependent. The objection is withdrawn. However, claims 5 and 6 are now objected to as depending from a rejected claim, but would otherwise be allowable if rewritten in independent form including all of the limitations of the claim(s) from which they depend.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 18 is drawn to vector comprising the plasmid 'pCAGGS'. The specification does not teach how to make pCAGGS, and the plasmid sequence is not disclosed. Because the plasmid is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification of otherwise readily available to the public, or there is a failure to meet the enablement requirement. Because the specification fails to set forth such a method, and it is not apparent that the plasmid is readily available to the public, claim 18 is not enabled, see 37 C.F.R. 1.801-1.809.

The rejection can be overcome by deposit of the plasmid with a depository recognized under the Budapest Treaty, and compliance with 37 C.F.R. 1.801-1.809. If a deposit is made under the conditions of the Budapest Treaty, then filing of an affidavit or declaration by Applicants or Assignees, or a statement by an attorney of record over his or her signature and registration number, stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository, is required. This requirement is necessary when a deposit is made under the provisions of the Budapest Treaty as the treaty leaves this specific matter to the discretion of each State.

If a deposit is not made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. 1.801-1.809, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request for the effective life of the patent, whichever is longer; and;

(d) a test of the viability of the biological material at the time of deposit (see 37 C.F.R. 1.807); and;

(e) the deposit will be replaced if it should ever become inviable.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 4, 17, 19, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al (Biotech. Bioeng. 69(4): 418-428, 2000) in view of Conrad et al (J. Biol. Chem. 264(29): 17368-17373, 1989).

Kim taught that glucagon, including residues 19-29, can serve as a binding partner for affinity chromatographic purification of recombinantly-expressed fusion proteins. Kim exemplified a prokaryotic expression vector encoding a fusion of glucagon to the N-terminus of IL-2, and purification of the expressed fusion protein on an affinity column comprising a glucagon receptor. The protein of interest can be separated from the glucagon purification tag by enterokinase cleavage. See abstract; Fig. 1 on page 420; Affinity Column Chromatography (bridging columns 1 and 2 on page 421; paragraph bridging pages 424 and 426; Fig. 5 on page 425; and paragraph bridging pages 427 and 428.

Kim did not teach a mammalian expression vector.

Conrad taught mammalian expression vectors encoding IL-2, as well as expression of IL-2 in mammalian cells, and subsequent purification by multiple chromatographic steps taking 3 days. See abstract; page 17368, column 1, lines 1-10; and page 17370, column 2, "Purification of recombinant human IL-2".

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the purification method of Conrad by expressing IL-2 in mammalian cells as a fusion to glucagon, as taught by Kim. One would have been motivated to do so because the method of Kim allows a single step purification of the fusion protein (see Affinity Column Chromatography (bridging columns 1 and 2 on page 421), and so is

much simpler. One of ordinary skill appreciates that mature, glycosylated IL-2 can be separated easily by enterokinase cleavage and repassage through the affinity column to remove the cleaved glucagon affinity tag. Thus the invention as a whole was prima facie obvious.

Claims 1-4, 17, 19, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al (Biotech. Bioeng. 69(4): 418-428, 2000) in view of Conrad et al (J. Biol. Chem. 264(29): 17368-17373, 1989) and Saunders et al (US 5486599).

The teachings of Kim and Conrad are discussed above. These references render obvious a mammalian expression vector encoding a fusion protein comprising IL-2 with a glucagon purification tag attached to the N-terminus of IL-2.

These references do not teach a fusion protein with glucagon attached to the C-terminus of IL-2.

It would have been obvious to one of ordinary skill in the art at the time of the invention to construct a fusion protein comprising a glucagon purification tag at either the N- or C-termini of IL-2, or any other protein of interest. The terminus at which the fusion is made is simply a matter of design choice, as evidenced by Saunders who indicated that that affinity purification tags can be placed either terminus. See column 26, lines 33-41. Thus the invention as a whole was prima facie obvious.

Claims 1-4, 17, 19, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al (Biotech. Bioeng. 69(4): 418-428, 2000) in view of Dorai et al (BIO/TECHNOLOGY 12: 890-897, 1994).

Kim taught that glucagon, including residues 19-29, can serve as a binding partner for affinity chromatographic purification of recombinantly-expressed fusion proteins. Kim exemplified a prokaryotic expression vector encoding a fusion of glucagon to the N-terminus of human IL-2, and purification of the expressed fusion protein on an affinity column comprising a glucagon receptor. The protein of interest can be separated from the glucagon purification tag by enterokinase cleavage. See abstract; Fig. 1 on page 420; Affinity Column Chromatography (bridging columns 1 and 2 on page 421; paragraph bridging pages 424 and 426; Fig. 5 on page 425; and paragraph bridging pages 427 and 428.

Kim did not teach a mammalian expression vector encoding a fusion protein.

Dorai taught mammalian expression vectors encoding single-chain Fv antibody proteins with C-terminal fusions to affinity purification tags such as the B domain of protein A (FB protein), S-peptide, and hexa-histidine. See abstract; and page 894, column 1, first paragraph through column 2, first full paragraph; paragraph bridging pages 896 and 897; and first full paragraph on page 897.

With regard to claims 1 and 2 alone, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the glucagon affinity purification tag of Kim for any of the purification tags of Dorai. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted,

one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). This substitution would result in a mammalian expression vector comprising a nucleic acid encoding a fusion protein comprising glucagon at the C-terminus.

Further, in consideration of claims 1-4, the references can be combined as follows. It would have been obvious to one of ordinary skill in the art at the time of the invention to express the IL-2/glucagon fusion protein of Kim from the mammalian expression vector of Dorai in the mammalian cells of Dorai. One would have been motivated to do so because human IL-2 is a glycoprotein, and one of ordinary skill appreciates that prokaryotes, including the E.coli expression host of Kim, do not support polypeptide glycosylation. Thus in order to express a more authentic, glycosylated form of IL-2, one of ordinary skill would be motivated to use a mammalian expression vector and host, as taught by Dorai. In view of the combined teachings of Kim and Dorai regarding the N- or C-terminal positioning of the purification tag, it would have been obvious to one of ordinary skill in the art at the time of the invention to place the purification tag at either terminus of the protein of interest.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 11/1/07 have been fully considered but they are not persuasive.

Applicant addresses the obviousness rejections at pages 16-23 of the response. Applicant's discusses the Kim reference at length with regard to protein purification from inclusion bodies formed in prokaryotic expression hosts. This discussion is not relevant to the rejection because the rejection depends on Kim for teaching the use of glucagon as a purification tag, and not for expression in E. coli. The rejection indicates that it would have been obvious to use the purification tag of Kim in the expression methods and vectors of Conrad and/or Dorai. Because the methods and vectors of Conrad and Dorai are used with/in mammalian cells, the issues associated with inclusion bodies do not arise. Applicant has presented no evidence that the glucagon purification tag of Kim could not be used for affinity purification of proteins expressed in mammalian cells, nor has Applicant presented any evidence or logic to indicate that the use of such a tag would not be reasonably expected to simplify the purification of IL-2.

In addressing the motivation stated in the rejection for using mammalian cells instead of prokaryotic cells (i.e. obtaining correct glycosylation) Applicant argues that the "skilled artisan would also recognize that Kim *et al.* would not delve into the issues of correct glycosylation of a protein, since *E. coli* does not have the physical mechanisms to produce glycosylated protein as does a mammalian-based cell line." This is essentially an admission that one of skill understands that in order to obtain proper glycosylation of IL-2, one needs to use a mammalian host. This is precisely why

one would be motivated to do so. Absent some evidence to the contrary, Applicants arguments that there is insufficient motivation to combine the references are unpersuasive. Clearly one would be motivated to do so in order to obtain correct glycosylation of IL-2.

Applicant argues at page 21 that the purification scheme for isolating the fusion protein from mammalian cells would be different than that used by Kim since proper folding and glycosylation would be expected. This is unpersuasive because Applicant presented no evidence that one would not be able to take an extract of the mammalian cells comprising the fusion protein and subject it to affinity chromatography to purify the fusion protein. The primary difference in the purification scheme would be that the refolding steps discussed at pages 17-21 of the response would be unnecessary since, as Applicant points out, the fusion protein would be expected to be properly folded.

At page 22 Applicant asserts that the Examiner proposes the use of E. coli as an expression host in the rejection over Kim and Connor. This is incorrect. The rejection clearly states that it would have been obvious to use mammalian cells. It does not propose the use of E. coli as an expression host.

At pages 22 and 23 Applicant argues that the cited references do not render obvious the claims as amended because they do not teach a fusion protein comprising a peptide that has the sequence of SEQ ID NO: 1. This is unpersuasive, glucagon is a peptide that has the sequence of SEQ ID NO: 1, i.e. amino acids 19-29 of glucagon. The claims as written do not exclude a fusion protein comprising amino acids 1-29 of glucagon attached to a peptide of interest. The claim language "comprising a first

peptide that has the amino acid sequence shown in SEQ ID NO: 1" is open with respect to what is comprised in the peptide. Accordingly it embraces full-length glucagon.

Applicant appears to argue at page 23 that the invention provides unexpected results because the glucagon 19-29 peptide (SEQ ID NO:1) does not have any physiological activity and should not be immunogenic. This is unpersuasive as regards the rejection because, as discussed above, the claims are not limited to a peptide consisting of SEQ ID NO: 1, but instead embrace a peptide comprising full-length glucagon. Evidence of unexpected results must be commensurate in scope with the claims (See MPEP 716.02(d)). Also there is no evidence that one of ordinary skill would not expect glucagon, or any fragment thereof to be immunogenic, i.e. the fact that glucagon or fragments thereof are nonimmunogenic is not unexpected because glucagon is well conserved in mammals, as Applicant points out at page 23 of the response.

For these reasons the rejections are maintained.

Conclusion

No claim is allowed.

This application contains claims 7-16 drawn to an invention nonelected with traverse in the reply filed on 11/1/07. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

(Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center.supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635